

Application of a Simple Diagonal Force Field to the Simulation of Cyclopentane Conformational Dynamics*

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ABSTRACT

Molecular dynamics simulations have been carried out on the cyclopentane molecule using a diagonal force field and the results compared with both experiment and a recent study which used the MM3 force field [W. Cui, F. Li, and N. L. Allinger, *J. Am. Chem. Soc.*, **115**, 2943 (1993)]. The current simulation resulted in an RMS pseudorotational velocity of 1036 deg/ps, compared to the model estimated value of 400 deg/ps and the MM3 result of 1700 deg/ps. The pseudorotation amplitude was calculated to be 0.46 ± 0.02 Å, compared to the experimental value of 0.48 Å and the MM3 value of 0.5 ± 0.03 Å. The two distinct average C—H bond lengths seen for the axial and equatorial conformations in the MM3 simulation were not observed. The energy barrier to passing through the planar conformation was calculated at 4.7 kcal/mol as compared to the experimental value of 5.2 kcal/mol and the MM3 value of 4.2 kcal/mol. During the simulation, the angle bending term dominated the potential energy, followed by the torsion energy, as was seen with MM3. The third largest energy term was the bond stretching, followed by the van der Waals interaction, the reverse of what was seen with MM3. The effects of carrying out the simulation under conditions of constant energy versus constant temperature are discussed. © 1996 by John Wiley & Sons, Inc.

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Introduction

Most of the molecular mechanical force fields in common use have been optimized for application either to small molecules or to biological macromolecules.¹⁻⁵ In the small molecule field, Allinger's MM2 and MM3 force fields² have served as the standard. These force fields have typically been applied to the highly accurate calculation of heats of formation, structures, conformational energies, and rotational barriers,² as well as to the "chemically accurate" calculation of vibrational frequencies, absolute entropies, and entropies of activation for internal rotation.⁶ The MM2 program⁷ allowed for minimization of structures, but until recently there was no capability for carrying out molecular dynamics (MD) calculations. With the development of MM3-MD,⁸ however, the MM3 force field can now be applied to MD simulations.

A recent study by Cui et al.⁹ examined the performance of the MM3 force field under the conditions of MD as applied to the pseudorotation of cyclopentane. This study was of interest to us, because just as the MM3 force field is being expanded to treat polypeptides and proteins¹⁰ and applied to MD simulations, this laboratory has been developing a second generation diagonal force field,¹¹⁻¹³ one of the goals of which is to be able to model the structural and conformational energetic properties of many small molecules to a "reasonable" degree of accuracy. The capability to model the conformational energies of small molecules on a level comparable to that of MM2/MM3 has already been demonstrated for simple unstrained molecules such as butane; methylethylthioether; methyl, ethyl, and propyl alcohol; methyl, ethyl, and propyl amine; and 1,2-ethanediol.¹² In one class of molecules studied, the dioxanes, the Weiner et al.¹ force field used with either the standard ESP¹⁵ or new RESP^{12,13} charge model actually significantly outperformed MM2 and MM3.¹⁴

Most molecular mechanical force fields partition the energy of a system into common components: the strain energy associated with bonds and angles which are distorted from their equilibrium values, the quantum mechanical effects represented by the dihedral term, and the electrostatic and van der Waals interactions between atoms in different molecules or atoms in the same molecule which

are separated by at least two bonds. The way this energy is actually partitioned for a given system is highly variable among force fields, with the bond and angle components probably being the most well defined and the remaining components being highly interdependent.

Because of its emphasis on the highly accurate representation of structures and vibrational frequencies, the MM2/MM3 force fields have a relatively complicated energy expression as compared to the macromolecular force fields. MM3 includes higher order terms (beyond the harmonic approximation) for both the bond and angle energies as well as cross-terms coupling bond-angle, bond-torsion, and angle-angle distortions. The Weiner et al.¹ (AMBER) force field, on the other hand, was originally developed for modeling the energetics and structures of proteins and DNA and so there the emphasis was on the accurate representation of the electrostatic interactions. Bond and angle energies are represented in AMBER using the harmonic approximation and no cross-terms are included. The parameters from each force field which are relevant to cyclopentane are presented in Table I.

Only a limited number of force field comparisons have appeared in the literature,^{16,17} and as the domains of the MM3 and macromolecular force fields begin to overlap more and more, this is perhaps an appropriate time to assess the strengths and weaknesses of the different approaches. We thus decided to follow the lead of Cui et al.,⁹ and carry out our own MD simulation of cyclopentane, so that we might compare the results obtained with a simple diagonal force field with those obtained using MM3. Because this study is meant to serve as a comparison, we have based the analysis and most of the figures on the study by Cui et al.⁹

Cyclopentane is a simple molecule which lends itself well to a force field study such as this. It contains only two different atom types. Its conformational space is limited by its cyclic structure. The planar conformation is not favored because of the eclipsing of the ring dihedral angles. In fact, cyclopentane is known to have two degenerate low energy conformations.¹⁸ The bent conformation possesses C_s symmetry and consists of four of the carbons in a plane with the fifth carbon bent out of the plane. The twisted conformation possesses C_2 symmetry and consists of three contiguous carbons forming a plane about which the remaining two carbons twist to be situated symmetrically above and below.

TABLE I.
Comparison of Weiner et al.^a and MM3^b Force Field Parameters for Cyclopentane.^{c,d,e}

Force field					
Weiner et al. ¹			MM3 ²		
Bond	k_r	r_0	Bond	k_s	r_0
CT—CT	310	1.526	C—C	323	1.5247
CT—HC	331	1.090	C—H	337	1.1120
Angle	k_θ	θ_0	Angle	k_θ	θ_0
CT—CT—CT	40	109.50	C—C—C	48	111.00
CT—CT—HC	35	109.50	C—C—H	42	109.31
HC—CT—HC	35	109.50	H—C—H	40	107.60
Dihedral			Dihedral		
X—CT—CT—X	V_3 :	1.3	C—C—C—C	V_3 :	1.160
	V_2 :	0.0		V_2 :	0.170
	V_1 :	0.0		V_1 :	0.185
			C—C—C—H	V_3 :	0.280
				V_2 :	0.000
				V_1 :	0.000
			H—C—C—C	V_3 :	0.238
				V_2 :	0.000
				V_1 :	0.000
			Stretch-bend	$k_{s\theta}$	
			C—C—C	0.13	
			C—C—H	0.08	
			H—C—H	0.00	
			Torsion-stretch	$k_{\omega s}$	
			C—C	0.059	
			Bend-bend	$k_{\theta\theta}$	
			C—C—C	0.24	
			C—C—H	0.30	
			H—C—H	0.00	
VDW	R^*	ϵ	VDW	R^*	ϵ
CT	1.80	0.06	C	2.04	0.027
HC	1.54	0.01	H	1.62	0.020

^aRef. 1.^bRef. 2.^cEquilibrium bond distances in Å, angles in degrees. Force constants in kcal/mol. van der Waals radii in Å, well depths in kcal/mol.^dThe MM3 equilibrium angle parameters depend on the degree of substitution of the central C. The MM3 angle-bending, dihedral, and stretch-bend parameters are specific for a five-membered ring.^eThe MM3 V_2 dihedral component has a phase shift of 90°.

Because of the fivefold symmetry of the cyclopentane molecule, these two low energy conformations can be formed with different sets of atoms, and the molecule interconverts between them via a process called pseudorotation. In pseudorotation the endocyclic dihedral angles vary in a concerted fashion, with the angle of maximum pucker pass-

ing around the ring.¹⁸ The wavelike movement of the puckering around the ring is modulated by a radial vibration which causes the degree of puckering to oscillate about an equilibrium value.¹⁸ The movement is not a true rotation since the motion of the atoms is perpendicular to the direction of the rotation.¹⁸

Methods

The calculations were carried out using the Weiner et al. all-atom force field¹ and the AMBER 4.0 package.¹⁹ The cyclopentane molecule was first equilibrated for 50 ps at a constant temperature of 298 K using a coupling constant of 0.2 ps.²⁰ Next, a constant energy run was carried out using the final coordinates and velocities from the constant temperature run. This final set of coordinates and velocities was fortuitously very close to the target temperature of 298 K, otherwise it would have been necessary to choose another set from near the end of the equilibration with the desired temperature. The constant energy run consisted of 10 ps of equilibration followed by data collection between 10 and 20 ps.

A second set of data was collected at a constant temperature of 298 K. This run was also started from the final set of coordinates and velocities from the 50 ps of equilibration at constant temperature. The temperature coupling constant was set to 0.2 ps for the 50 ps of equilibration and for the 10 ps of data collection.

A third set of data was collected at a constant temperature of 298 K, but with the coupling constant relaxed to 0.5 ps. This run was equilibrated for 50 ps starting from the final set of coordinates and velocities from the initial 50 ps of equilibration at constant temperature. Data were then collected for 10 ps.

A fourth set of data was collected at a constant temperature of 293 K with a coupling constant of 0.2 ps. This run was equilibrated for 20 ps starting with the final set of coordinates and velocities from the previous run. Data were then collected for 10 ps.

Fifth and sixth sets of data were collected at a constant temperature of 298 K with the coupling constants relaxed to 0.9 and 2.0 ps, respectively. These runs were equilibrated for 50 ps starting from the final set of coordinates and velocities from the initial 50 ps of equilibration at constant temperature. Each equilibration was followed by 10 ps of data collection.

A time step of 0.02 fs was employed for all simulations. The 1–4 electrostatic and van der Waals interactions were scaled by one half. A constant dielectric of 1.0 was employed and all nonbonded interactions were included. AMBER uses the leapfrog algorithm for molecular dynam-

ics integration. Coordinates were collected every 100 steps.

The pseudorotation phase angle, P , was calculated according to the formula of Altona et al.²¹ as a function of the five endocyclic torsion angles:

$$\tan P = [(\theta_2 + \theta_4) - (\theta_1 + \theta_3)]/2\theta_0(\sin 36 + \sin 72)$$

The puckering amplitude, q , is also determined as a function of the five endocyclic torsion angles, and represents the deviation from planarity of the ring:

$$q = \theta_m/102.5$$

where

$$\theta_m = 2/5\sqrt{(\sum \theta_j \cos \alpha_j)^2 + (\sum \theta_j \sin \alpha_j)^2}$$

and

$$\alpha_j = 4\pi_j/5$$

and the sum is taken over the five endocyclic torsion angles.

Results

CONFORMATIONAL INTERCONVERSION VIA PSEUDOROTATION

The one major difference in protocol between our study and that of Cui et al.⁹ was that we carried out both constant temperature and constant energy simulations, in order to compare the two approaches, whereas their study was limited to constant temperature simulations. Because one of the goals of the study was to calculate kinetic parameters, a constant energy approach seemed more logical to us. Temperature coupling schemes can affect the dynamics of the system under study, which is usually acceptable when one is focusing on energetic properties, but less desirable for a dynamics study. In the event that the frequency of the temperature coupling is some multiple value of the frequency of one of the motions intrinsic to the system, anomalous effects can be introduced.

Furthermore, the temperature is well behaved for a system such as this with no nonbonded cutoff. The average temperature during the 10 ps of data collection for the first constant temperature run was 298.3 K and the standard deviation was 32.4 K. This compares to an average temperature of 293.0 K with a standard deviation of 38.9 K for the constant energy run. Figure 1 plots the value of one of the endocyclic torsion angles as a function of time from the constant energy simulation. The

pseudorotation phase angle was also calculated for this simulation. Both are measures of conformational conversion and both exhibit the same frequency of about 2.5 cyc/ps—or half of the MM3 value of 5 cyc/ps.⁹ The pseudorotation amplitude was also calculated as a function of time. The average value is calculated to be 0.46 Å with a standard deviation of 0.02 Å. This compares well with the experimental value of 0.48 Å from Raman spectroscopic studies.²² The value reported from the MM3 simulation was 0.5 ± 0.03 Å.⁹

KINETICS

The pseudorotational velocity can be calculated as the change in pseudorotational phase angle with time. The RMS pseudorotational velocity from the constant energy simulation is calculated as 1036 deg/ps. Cui et al. reported an RMS value of 1700 ± 300 deg/ps from the MM3 simulation.⁹ Both the MM3 and AMBER values are in good agreement with the model estimated value of 400 deg/ps,²³ which is calculated as a function of the experimentally determined reduced mass and assumes that there is no significant energy barrier associated with pseudorotation.

ENERGETICS

The average value of the instantaneous potential energy in the constant energy simulation is about 18 kcal/mol, which differs from the average value of 25 kcal/mol seen with MM3, however, such molecular mechanical energies are only relevant in terms of differences seen with a particular

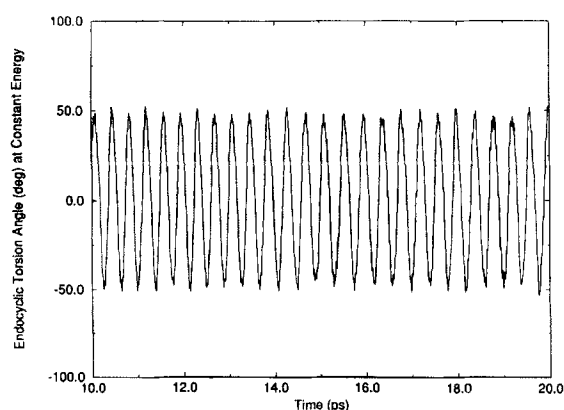


FIGURE 1. The value of a particular endocyclic torsion angle is plotted against time for the constant energy simulation. One cycle of rotation for the torsion is equivalent to one complete cycle of pseudorotation.

force field. The components of the potential energy over the course of 1 ps are shown in Figure 2. It is interesting to compare the contributions of the various components with those seen with MM3,⁹ where the angle bending energy contributed 11–12 kcal/mol; torsion energy ~ 8 kcal/mol, van der Waals ~ 5 kcal/mol; bond stretching ~ 3 kcal/mol; and the bend–bend, stretch–bend, and torsion–stretch energies were 1 kcal/mol or less. The Weiner et al.¹ force field energy components were ~ 8 kcal/mol for the angle bending, ~ 6 kcal/mol for the torsion, ~ 4 kcal/mol for the bond stretching, ~ 1 kcal/mol for the van der Waals, and essentially 0 kcal/mol for the electrostatic interactions. Thus, with both force fields the angle energy dominated, followed by the torsion, but the order of the bond and van der Waals contributions were reversed.

At this point it is worth pointing out one of the major differences between the Weiner et al.¹ force field and MM2/MM3 force fields.² The MM2 and MM3 force fields employ bond dipoles to determine the electrostatic interactions for a system, whereas the Weiner et al.¹ and Cornell et al.¹¹ force fields use atom-centered point charges which are calculated to reproduce the electrostatic potential surface of the molecule. The MM3 simulation of cyclopentane had an electrostatic contribution to the potential energy of absolutely zero because the two different types of bonds present in this system have bond dipole moments equal to zero. The ESP fit charges used by AMBER, however, did have finite values. The carbon charge was equal to

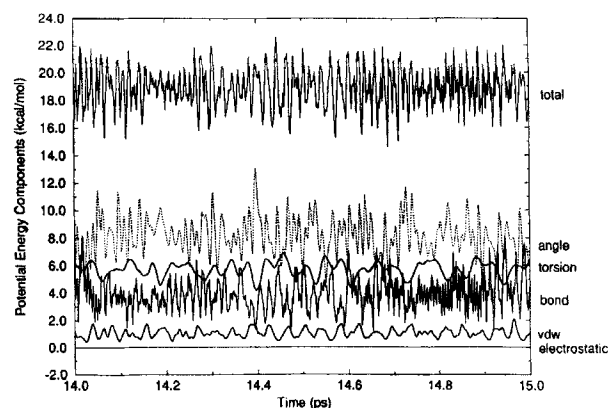


FIGURE 2. Components of the potential energy for the constant energy simulation plotted over 1 ps. The angle and torsion components are the first and second largest, as was seen in the MM3 simulation. The third largest component is from the bond energy, in contrast to the MM3 simulation where it was the van der Waals energy.

-0.0074 and the hydrogen charge was equal to 0.0037 . Because the charges were so small, however, the total electrostatic energy for the system was very nearly equal to zero as one would expect with a hydrocarbon.

Another aspect of the conformational energetics of cyclopentane which can be investigated is the energy barrier to pass through the planar conformation. This barrier has been determined to be 5.2 kcal/mol by experiment.²⁴ The Weiner et al. force field¹ calculates the barrier at 4.7 kcal/mol compared to the MM3 value of 4.2 kcal/mol. Using our new force field,¹¹ which has a higher value for the $X-CT-CT-X$ V_3 torsional parameter of 1.4 kcal/mol compared to the previous value of 1.3 kcal/mol, we obtain a barrier of 4.9 kcal/mol. (The new value of the dihedral parameter was adjusted to fit the rotational barrier for ethane.)

COOPERATIVE MOVEMENT IN PSEUDOROTATION

The coupling of the C—H bond lengths to the pseudorotation process can also be explored. A plot of C—H bond length versus time for the MM3 simulation showed that the bond length varied about two distinct average values during one cycle of pseudorotation. In the AMBER constant energy simulation, however, the bond varied about one average value. The length of a particular C—H bond is plotted against time in Figure 3. The magnitude of the bond length variation is clearly modulated by a lower frequency motion—that of the

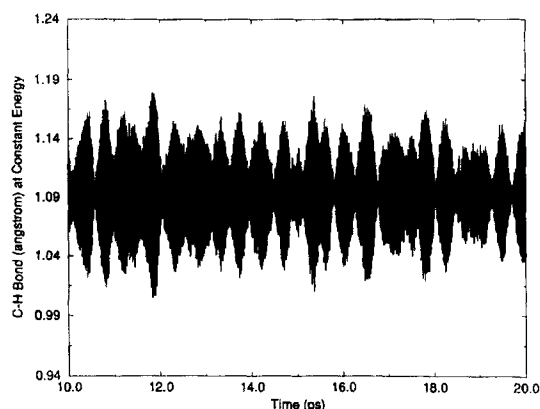


FIGURE 3. An arbitrary C—H bond length is plotted against time for the constant energy simulation. The bond-stretching motion is clearly modulated by a lower frequency motion, thus demonstrating the coupling between the bond-stretching and the pseudorotation process.

pseudorotation. Cui et al.⁹ attributed the bimodal distribution seen in their simulation to the existence of two different equilibrium values for the C—H bond, depending on whether the hydrogen was in an axial or equatorial position, as supported by experimental evidence.^{22,25,26}

The inability of the simulation reported here to reproduce this effect may be due to the use of a simple harmonic function for calculating the bond energy in the Weiner et al.¹ force field versus the use of an anharmonic function in MM2/MM3, which employs higher ordered terms. The C—H bond length is longer when the hydrogen is in an axial position, due to transannular repulsion of axial hydrogen atoms. It is possible that the simple bond expression is unable to reproduce this fairly subtle effect (the two equilibrium bond lengths differ by 0.005 Å in the MM3 study).⁹

COMPARISON OF CONSTANT ENERGY AND CONSTANT TEMPERATURE SIMULATIONS

We chose to carry out our simulation at constant energy to avoid perturbing the trajectory of the molecule through the scaling of atomic velocities during a constant temperature simulation. As noted above, the temperature remained very close to the desired value of 298 K during the constant energy simulation, and the standard deviation of the temperature was not much greater than that seen with a constant temperature simulation. The first constant temperature simulation was carried out at a temperature of 298 K with a coupling constant of 0.2 ps. Berendsen et al. recommended the use of coupling constants in the range of 0.1 – 0.4 ps; however, this conclusion was based on simulations carried out on liquid water with a non-bonded cutoff.²⁰ This trajectory exhibited a pseudorotational velocity of 3.0 cyc/ps, in contrast with the velocity of 2.5 cyc/ps observed during the constant energy simulation. The pseudorotation amplitude exhibited an average value of 0.47 ± 0.02 Å as compared to the value of 0.46 ± 0.02 Å observed during the constant energy run. The variation of C—H bond length with time is more uneven than in the constant energy simulation.

A second constant temperature simulation was run with a coupling constant of 0.5 ps to the constant temperature bath. The velocity of pseudorotation is not reduced by much with the looser coupling constant, having a value of about 2.9 cyc/ps. Since the average temperature of the constant energy run was actually 293 K rather than

298 K, we ran a third constant temperature simulation with a coupling constant of 0.2 ps and a target temperature of 293 K. Under these conditions, the pseudorotational velocity is still calculated to be about 2.9 cyc/ps. From this we concluded that the different pseudorotational velocities seen between the constant temperature and constant energy simulations are due to the constant temperature protocol rather than the small difference in temperature.

We tested this hypothesis further by carrying out three additional constant temperature runs with successively looser coupling constants. The fourth constant temperature simulation was carried out with a target temperature of 298 K and a coupling constant of 0.9 ps. This simulation exhibited a pseudorotational velocity of 2.9 cyc/ps as well. The fifth and sixth constant temperature runs were carried out with target temperatures of 298 K and coupling constants of 2.0 and 20.0 ps, respectively. The pseudorotational velocity calculated for these simulations was 2.7 cyc/ps, reflecting a return to conditions which are similar to constant energy, due to the weak coupling to the bath.

It is therefore clear that carrying out MD simulations of cyclopentane under conditions of constant temperature can affect the calculated pseudorotational velocity by up to 20% when the coupling constant is within the range recommended by Berendsen et al.²⁰ Cui et al. carried out their simulations with a coupling constant of 0.1 ps (personal communication) and it is possible that the higher pseudorotational velocity that they witnessed resulted partly from the constant temperature protocol. The pseudorotational velocities calculated by MM3 (5.0 cyc/ps) and AMBER (2.5 cyc/ps) differ by more than 20%, suggesting that other differences between the two simulations such as the force field employed are also affecting the kinetics.

Conclusion

We have carried out MD simulations of the cyclopentane molecule under conditions of both constant energy and constant temperature using the Weiner et al.¹ force field and compared the results to those reported by Cui et al.⁹ using MM3. The pseudorotation process was found to be well reproduced using the Weiner et al.¹ force field in terms of velocity and puckering amplitude. In addition, the barrier to passing through the planar conformation was calculated at 4.7 kcal/mol as compared to the experimental value of 5.2

kcal/mol and the value of 4.2 kcal/mol calculated with the MM3 force field. The Weiner et al. force field¹ was unable, however, to reproduce the subtle differences in C—H bond length seen between the axial and equatorial positions. We found that carrying out the simulation under conditions of constant temperature, even with a fairly loose coupling constant, increased the observed pseudorotational velocity. We conclude that the Weiner et al.¹ force field, although simpler in form than the MM3 force field, performs quite well at reproducing the conformational dynamics and energetics of this small molecule in the gas phase.

Note

Supplementary material consisting of additional figures analogous to those found in Ref. 9 is available from the authors upon request or via the Internet (see footnote * on page 1541).

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